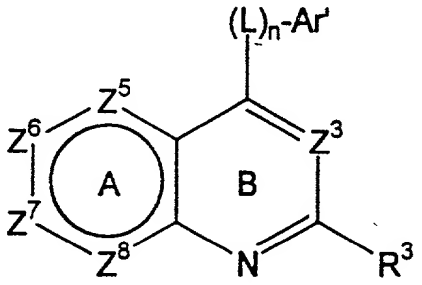
Claims

1. A method to treat conditions characterized by enhanced p38-α activity and/or enhanced TGF-β activity, which method comprises administering to a subject in need of such treatment a compound of the formula:



(1)

or the pharmaceutically acceptable salts thereof

wherein R^3 is a noninterfering substituent;

each Z is CR^2 or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N;

each R^2 is independently a noninterfering substituent;

L is a linker;

n is 0 or 1; and

Ar' is the residue of a cyclic aliphatic, cyclic heteroaliphatic, aromatic or heteroaromatic moiety optionally substituted with 1-3 noninterfering substituents.

2. The method of claim 1 wherein said condition is a proinflammation response or a fibroproliferative response or both.

3. The method of claim 2 wherein said proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory

disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, or pyresis.

4. The method of claim 2 wherein said fibroproliferative response is associated with a renal disorder, a vascular disorder, a fibrosis, an autoimmune disorder, an eye disease, excessive scarring, a neurological condition, myelofibrosis, tissue thickening, nasal polyposis, a polyp, liver cirrhosis, or osteoporosis.

5. The method of claim 4 wherein said renal disorder, is glomerulonephritis, diabetic nephropathy, renal interstitial fibrosis, renal fibrosis in transplant patients receiving cyclosporin, and HIV-associated nephropathy; and

wherein said vascular disorder is progressive systemic sclerosis, polymyositis, scleroderma, dermatomyositis, eosinophilic fascitis, morphea, or Raynaud's syndrome; and

wherein said fibrosis is associated with adult respiratory distress syndrome, idiopathic pulmonary fibrosis, interstitial pulmonary fibrosis, cardiac fibrosis, keloid formation, or hypertrophic scarring; and

wherein said autoimmune disorder is systemic lupus erythematosus, scleroderma, or rheumatoid arthritis; and

wherein said eye disease is retinal detachment, cataracts, or glaucoma; and

wherein said neurological condition is CNS injury, Alzheimer's disease, or Parkinson's disease.

6. The method of claim 1 wherein R^3 is a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N.

7. The method of claim 6 wherein R^3 is alkyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each unsubstituted or substituted with 1-3 substituents.

8. The method of claim 7 wherein said substituents are independently selected from the group consisting of halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C) and with respect to any aryl or heteroaryl moiety, said group further including alkyl (1-6C).

9. The method of claim 1 wherein said substituents on substituted Ar' are independently selected from the group consisting of optionally substituted alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C),

and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C).

10. The method of claim 9 wherein Ar' is phenyl, 2-, 3-, or 4-pyridyl, 2- or 4-pyrimidyl, indolyl, isoquinolyl, quinolyl, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzofuranyl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, or morpholinyl, all of which may optionally be substituted.

11. The method of claim 1 wherein each R^2 is independently a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N.

12. The method of claim 11 wherein each R^2 is independently H, alkyl, alkenyl, alkynyl, acyl or hetero-forms thereof or is aryl, arylalkyl, heteroalkyl, heteroaryl, or

heteroarylalkyl, each unsubstituted or substituted with 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C),

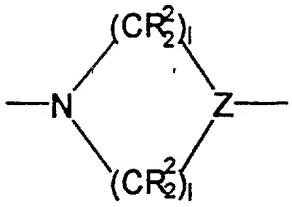
and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C), or

R_2 is selected from the group consisting of halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, NRSOR, $NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, NRSOR, $NRSO_2R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C).

13. The method of claim 11 wherein said substituents on R^2 are independently selected from the group consisting of R^4, halo, OR^4, NR^4_2, SR^4, $-OOCR^4$, $-NROCR^4$, $-COOR^4$, R^4CO, $-CONR^4_2$, $-SO_2NR^4_2$, CN, CF_3, and NO_2, wherein each R^4 is independently H, or optionally substituted alkyl (1-6C), or optionally substituted arylalkyl (7-12C) and wherein two R^4 or two substituents on said alkyl or arylalkyl taken together may form a fused aliphatic ring of 5-7 members.

14. The method of claim 1 wherein n is 0 or n is 1 and L is a bivalent residue that provides a distance of 2-8Å between ring B and Ar'.

15. The method of claim 14 wherein L is $S(CR^2_2)_m$, $-NR^1SO_2(CR^2_2)_l$, $SO_2(CR^2_2)_m$, $SO_2NR^1(CR^2_2)_l$, $NR^3(CR^2_2)_m$, $NR^1CO(CR^2_2)_l$, $O(CR^2_2)_m$, or $OCO(CR^2_2)_l$,



wherein Z is N or CH and wherein m is 0-4 and l is 0-3;

R^1 is H, alkyl or arylalkyl where the aryl moiety may be substituted by 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C);

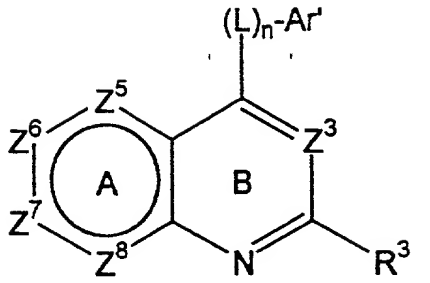
and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C); and

R^2 is as defined in claim 12.

16. The method of claim 1 wherein the compound of formula (1) is selected from the group consisting of compounds 1-87 herein.

17. The method of claim 1 wherein the compound of formula (1) is selected from the group consisting of compounds shown in Figures 1A-1C herein.

18. A pharmaceutical composition for treating conditions characterized by enhanced p38-α activity and/or enhanced TGF-β activity which composition comprises a therapeutically effective amount of a compound of the formula



(1)

or the pharmaceutically acceptable salts thereof

wherein R^3 is a noninterfering substituent;

each Z is CR^2 or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N;

each R^2 is independently a noninterfering substituent;

L is a linker;

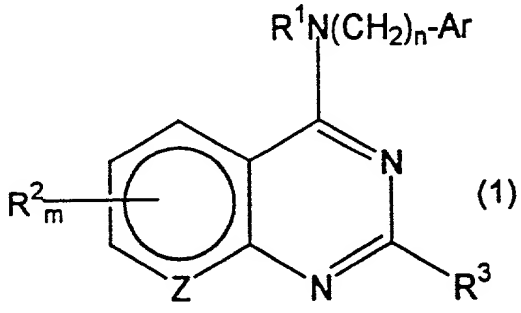
n is 0 or 1; and

Ar' is the residue of a cyclic aliphatic, cyclic heteroaliphatic, aromatic or heteroaromatic moiety optionally substituted with 1-3 noninterfering substituents in admixture with at least one pharmaceutically acceptable excipient.

19. The composition of claim 18 which further contains an additional therapeutic agent.

20. The composition of claim 19 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

21. A compound of the formula:



(1)

and the pharmaceutically acceptable salts thereof

wherein each R^2 is independently a noninterfering substituent;

m is an integer of 0-4;

Z is CH;

R^1 is alkyl (1-6C) or arylalkyl optionally substituted on the aryl group with 1-3 substituents independently selected from alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, $-SO_2NR_2$, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C);

n is 0, 1 or 2; and

(a) Ar is phenyl, substituted with at least one group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C), or pyridyl, indolyl, or pyrimidyl, each optionally substituted with at least one group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is a branched or cyclic alkyl group (5-7C) or is phenyl optionally substituted with 1-2 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, $-SO_2NR_2$, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); or

(b) Ar is phenyl, pyridyl, indolyl, or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is a branched or cyclic alkyl group (5-7C) or is phenyl substituted with 1-2 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, $-SO_2NR_2$, CN, and CF_3, wherein each R is independently H or lower alkyl (1-4C); or

(c) Ar is phenyl substituted with a group selected from the group consisting of optionally substituted NR_2, SR, -NROCR, RCO, -$CONR_2$, SO_2NR_2, CN, and CF_3, wherein each R is independently H or lower alkyl (1-4C); or pyridyl substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); or indolyl or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is a branched or cyclic alkyl group (5-7C) or is phenyl optionally substituted with 1-2 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, -SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); or

(d) Ar is phenyl, pyridyl, indolyl, or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C); and

R^3 is a branched or cyclic alkyl group (5-7C) or is phenyl substituted with 1-2 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, SR, -OOCR, -NROCR, RCO, -COOR, -$CONR_2$, -SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C).

22. The compound of claim 1 which is selected from the group consisting of

2-phenyl-4-(4-pyridylamino)-quinazoline;

2-(2-bromophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-chlorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-methylphenyl)-4-(4-pyridylamino)-quinazoline;

2-(4-fluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(3-methoxyanilyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-dichlorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-dibromophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-difluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;

2-(4-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-nitroquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino -6-aminoquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-7-aminoquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(3-methoxybenzylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methoxybenzylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(2-isobutylamino)-quinazoline; and

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methylmercaptobenzylamino)-quinazoline.